SSRI Effects on Pyschomotor Performance: Assessment of Citalopram and Escitalopram on Normal Subjects

MICHEL A. PAUL, GARY W. GRAY, RYAN J. LOVE, AND MARVIN LANGE

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Introduction: Standard aeromedical doctrine dictates that aircrew receiving treatment for depression are grounded during treatment and follow-up observation, generally amounting to at least 1 yr. The Canadian Forces has initiated a program to return selected aircrew being treated for depression to restricted flying duties once stabilized on an approved antidepressant with resolution of depression. The currently approved medications are sertraline (a selective serotonin reuptake inhibitor) and bupropion (noradrenaline and dopamine reuptake inhibitor). This study was undertaken to determine whether or not citalopram or escitalopram affect psychomotor performance. ***Method:*** In a double-blind crossover protocol with counter-balanced treatment order, 24 normal volunteer subjects (14 men and 10 women) were assessed for psychomotor performance during placebo, citalopram (40 mg), and escitalopram (20 mg) treatment. Each treatment arm lasted 2 wk, involving a daily morning ingestion of one capsule. There was a 1-wk washout period between medication courses. Subjects completed a drug side-effect questionnaire and were tested on three psychomotor test batteries once per week. ***Results:*** Neither citalopram nor escitalopram affected serial reaction time, logical reasoning, serial subtraction, multitask, or MacWorth clock task performance. ***Conclusions:*** While we found some of the expected side effects due to citalopram and escitalopram, there was no impact on psychomotor performance. These findings support the possibility of using citalopram and escitalopram for returning aircrew to restricted flight duties (non-tactical flying) under close observation as a maintenance treatment after full resolution of depression.

Keywords: citalopram, escitalopram, psychomotor performance, side effects.

BASED ON PREVIOUS work done at DRDC Toronto, Canadian Forces aircrew being treated for depression may be returned to restricted flying status while taking maintenance approved antidepressant medications after a 6-mo observation period following resolution of symptoms. Assessment by an aviation psychiatrist and neurocognitive testing are required. In addition to flying restrictions, significant geographic limitations apply, including limited deployability and a requirement for regular follow-up.

The preferred approved antidepressants for Canadian Forces aircrew have been bupropion and sertraline because of their minimal sedative qualities. Previous studies demonstrated neither of these medications had an adverse effect on psychomotor performance (13,14). Sertraline has some affinity for dopamine receptors (1) and bupropion for both dopamine and noradrenaline receptors (16). Citalopram and escitalopram are more specific serotonin receptors inhibitors and are widely used and efficacious in the treatment of depression (2,12,19) and other psychopathologies, including anxiety/panic disorder (9,17,18) and obsessive compulsive disorder (7,17). Citalopram is a 1:1 racemic mixture of R and S enantiomers, and escitalopram is the s-enantiomer. Citalopram was introduced in 1989 and escitalopram in 2003 after the expiration of the citalopram patent. Both are highly specific serotonin reuptake inhibitors with negligible effects on dopamine and noradrenaline receptor activity. Both have long half-lives (~30 h), allowing for once daily dosing and minimizing the risk for discontinuation syndrome with missed doses (5,11). Sedation and psychomotor effects are reportedly less prevalent than with other anti-depressants (20). In one study (15) citalopram was reported to reduce the number of correct responses on the Mackworth Clock Test, a vigilance task.

Citalopram and escitalopram are options to sertraline and bupropion in the treatment of depressed aircrew. The purpose of this study was to assess the effects on psychomotor performance of subacute administration of citalopram and escitalopram in normal clinical doses in healthy subjects. Because of the concerns about a vigilance effect, the Mackworth Clock Test (10) was included in the test battery.

METHODS

The study protocol was approved by the DRDC Toronto Human Research Ethic Committee. There were 24 normal volunteer subjects (14 men and 10 women) ranging from 21 to 57 yr of age. Their average age was 34.2 ± 11.3. All subjects provided written informed

From Defence Research & Development Canada–Toronto, North York, Ontario, Canada.

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Address reprint requests to: Michel A. Paul, M.Sc., Defence Research & Development Canada-Toronto, 1133 Sheppard Ave. West, P.O. Box 2000, North York, ON M3M 3B9, Canada; michel.paul@drdc-rddc.gc.ca.

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consent in compliance with the declaration of Helsinki. Before being accepted into the study all subjects passed a medical to screen out volunteers for whom these medications would not be appropriate (for example anyone taking psychotropic medications such as monamine oxidase inhibitors). Because these medications could be potentially harmful to a fetus, pregnant women were not allowed to participate and all female subjects were instructed to take precautions to avoid pregnancy during this study. Subjects were advised that in the event they required any other medication, prescription or over-the-counter, during the course of the study, they were to contact the principal investigator or a co-investigator prior to use of the medication except in the case of a medical emergency. Women using oral contraceptives or Depo-Provera were allowed to continue to do so through the study. All subjects were instructed that alcohol must be used in moderation when taking these medications and that alcohol must not be used within 24 h prior to each weekly psychomotor testing session. Coffee and other caffeinated beverages were not to be used in the 4 h immediately prior to psychomotor testing.

The design was a repeated-measures double-blind crossover protocol with three drug conditions: placebo, citalopram 40 mg, and escitalopram 20 mg. The order of medications was counterbalanced across subjects. The subjects took a single daily dose of placebo or citalopram or escitalopram in identical capsule format at home for 14 d. There was a 1-wk washout period between adjacent courses of medication. Preparation of the medications was contracted to a pharmacy. The subjects were evaluated in the laboratory for psychomotor performance once each week, on the same weekday, for the 9-wk protocol duration. During their weekly visit to the laboratory for psychomotor testing, the subjects also completed a weekly drug side effect questionnaire in which they were asked to rate symptoms on a Likert scale, including questions related to sleep hygiene issues, gastrointestinal symptoms, tremors, sweating, drowsiness, dizziness, and libido. In addition, during the psychomotor test sessions, subjects completed a computer-based questionnaire rating subjective sleepiness and fatigue.

The subjects were trained to asymptote performance on the psychomotor test batteries; a subset of the DRDC-Toronto SUSOPS battery involving serial reaction time, logical reasoning, and serial subtraction tasks, as well as a multitask (13,14) designed to simulate the information processing characteristics of flight performance. Because of the previously reported effects on

TABLE I. SUBJECTIVE SLEEPINESS AND FATIGUE SCORES COLLAPSED OVER WEEKS FOR CITALOPRAM, ESCITALOPRAM, AND PLACEBO.

Subjective Parameter	Citalopram	Escitalopram	Placebo
Sleepiness	2.74 ± 0.19*	2.77 ± 0.13*	2.29 ± 0.14
Mental fatigue	3.30 ± 0.26*	3.18 ± 0.20*	2.76 ± 0.25
Physical fatigue	3.27 ± 0.24*	3.13 ± 0.22*	2.70 ± 0.23

All values are mean ± SEM. *Significant differences relative to placebo. Score scale ranged from 1 to 7 with higher scores indicating more pronounced sleepiness/fatigue.

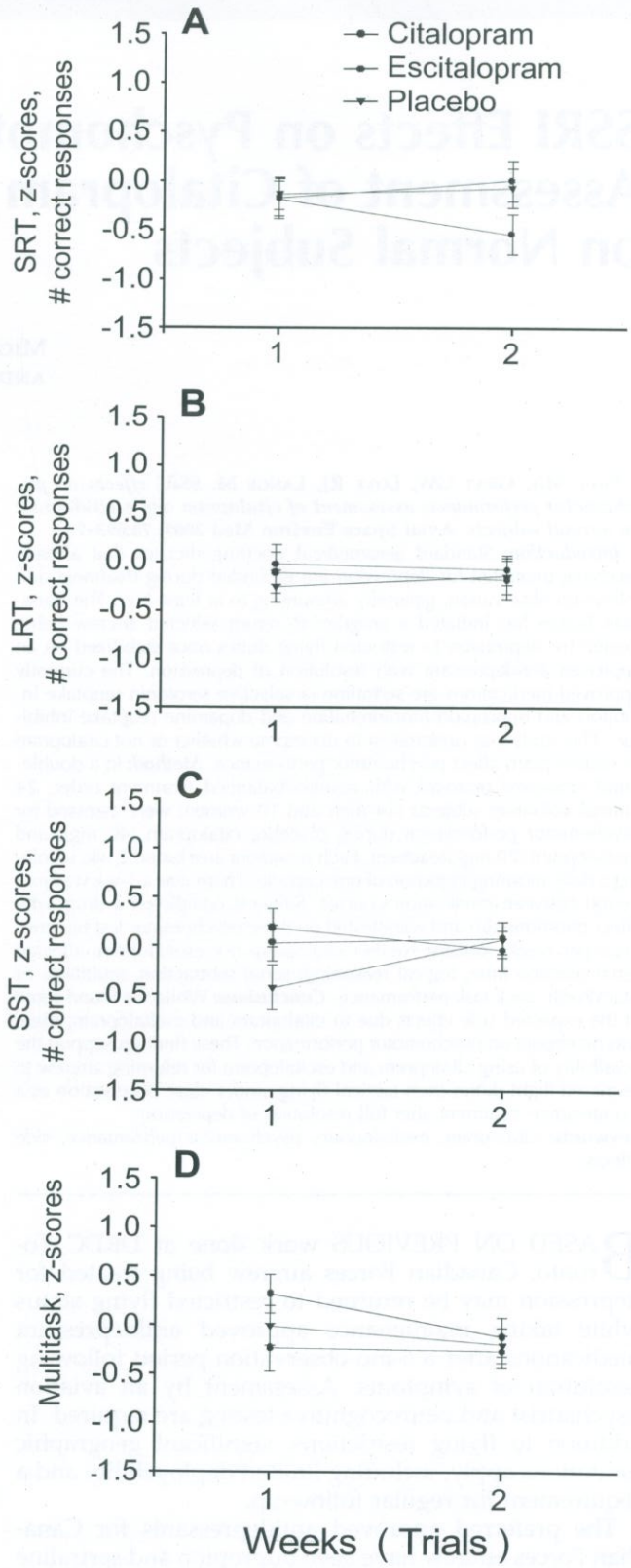

Fig. 1. Z-score transformations of number of correct responses to the A) serial reaction time (SRT), B) logical reasoning (LRT), and C) serial subtraction task (SST), and D) the Multitask score. All values are mean ± SEM and are plotted over weeks (trials).

vigilance, a recent version of the MacWorth Clock Test (10) was also included.

The dependent variables (number of correct responses for the SUSOPS tasks, "total score" for the multitask, and for the MacWorth Clock Task, number of correct responses, lapses, false alarms, and reaction time) were plotted over trials for each of the three 2-wk treatment sessions. The dependent variables from the questionnaires were also plotted over trials (weeks). Both the psychomotor and questionnaire data were submitted to 2-factor (3 levels of drugs × 2 levels of trials) repeated-measures analysis of variance. The Least Significant Difference test was used to assess planned comparisons. The acceptable level of significance for all main effects or interactions was 0.05.

RESULTS

Subjective Sleepiness and Fatigue

The subjective sleepiness and fatigue data are presented in **Table I**. There was a main effect of drugs for sleepiness [$F(2,464) = 5.49$, $p < 0.007$]. Post hoc testing of this main effect revealed that relative to placebo, both citalopram and escitalopram resulted in increased subjective sleepiness. There was also a drug × weeks interaction for sleepiness [$F(2,46) = 4.26$, $p < 0.02$]. Post hoc testing of this interaction revealed that escitalopram produced less sleepiness in week 2 than in week 1, and the sleepiness levels associated with citalopram did not change from week 1 to week 2. There were main effects of drugs for mental and physical fatigue. Post hoc testing of these two main effects revealed that relative to placebo, both citalopram and escitalopram resulted in elevated levels of subjectively assessed mental and physical fatigue. The drug × weeks interactions for mental and physical fatigue were not significant, indicating that for citalopram and escitalopram, mental and physical fatigue levels did not change from week 1 to week 2.

Psychomotor Data

A completely repeated-measures analysis of variance reduces overall variability by removing between-subjects differences from the error term. Note that all figures are graphed with z-scores in order to better demonstrate the within-subjects treatment effects. The analyses of variance were equivalent whether done with z-scores or with original units.

The Serial Reaction Time (SRT), Logical Reasoning Task (LRT), Serial Subtraction Task (SST), and Multitask performances are illustrated in **Fig. 1A–D**. There were no significant main effects of drugs or drug × weeks interaction for any of these four tasks. With respect to the MacWorth Clock Task, the number of correct responses, the number of misses, the number of false alarms, and reaction time are plotted in **Fig. 2A–D**. There were no significant main effects of drugs or drug × weeks interaction for any of the four MacWorth Clock Task data sets. These results indicate that neither citalopram nor escitalopram affect performance on any of the tasks used in this study.

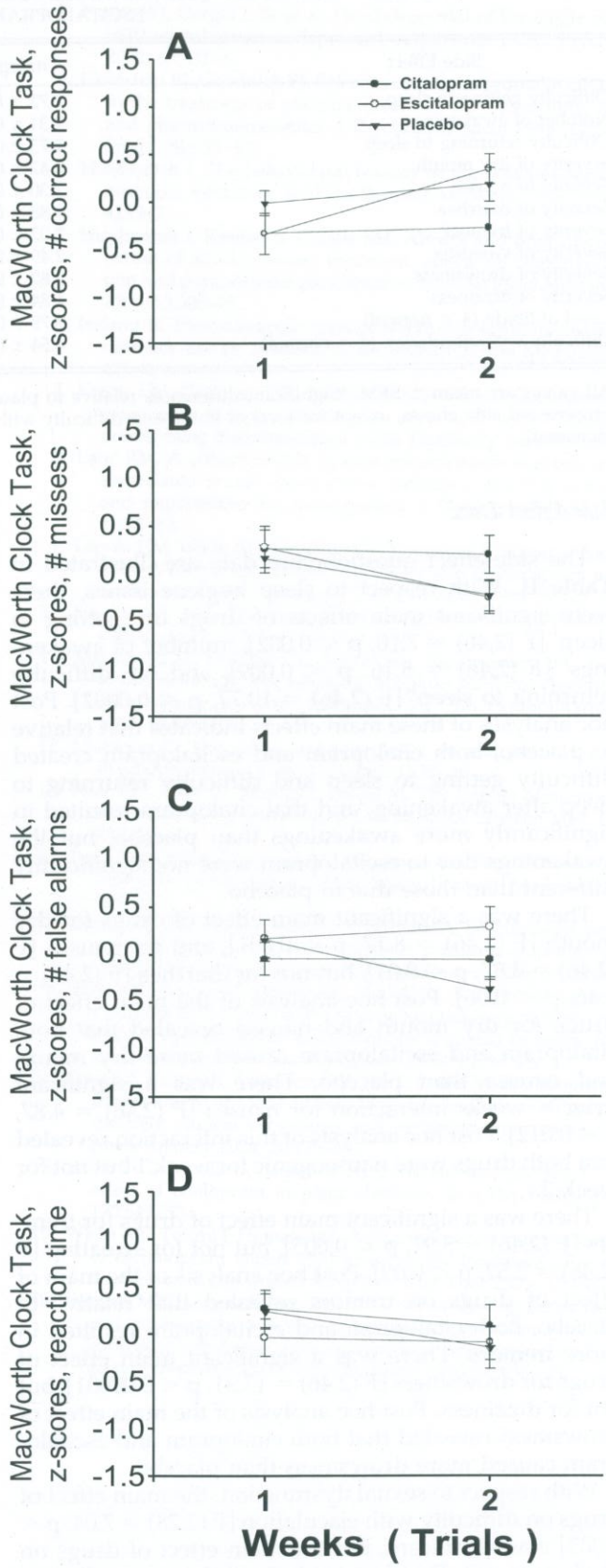

Fig. 2. Z-score transformations of the following MacWorth Clock Task parameters: A) number of correct responses, B) number of misses, C) number of false alarms, and D) reaction time. All values are mean ± SEM and are plotted over weeks (trials).

TABLE II. SIDE-EFFECT QUESTIONNAIRE SCORES AVERAGED OVER WEEKS FOR CITALOPRAM, ESCITALOPRAM, AND PLACEBO.

Side Effect	Citalopram	Escitalopram	Placebo
Difficulty getting to sleep	2.72 ± 0.34*	2.25 ± 0.32*	1.48 ± 0.19
Number of awakenings	2.31 ± 0.52*	1.76 ± 0.23	0.92 ± 0.19
Difficulty returning to sleep	2.73 ± 0.30*	2.26 ± 0.24*	1.46 ± 0.18
Severity of dry mouth	2.42 ± 0.33*	1.97 ± 0.23*	1.15 ± 0.06
Severity of nausea	2.30 ± 0.27*	1.86 ± 0.22*	1.25 ± 0.21
Severity of diarrhea	1.88 ± 0.20	2.05 ± 0.25	1.44 ± 0.16
Severity of tremors	2.02 ± 0.30*	1.92 ± 0.25*	1.08 ± 0.07
Severity of sweating	2.49 ± 0.32	2.26 ± 0.26	1.85 ± 0.23
Severity of drowsiness	3.82 ± 0.33*	3.21 ± 0.31*	1.77 ± 0.19
Severity of dizziness	1.84 ± 0.20	1.92 ± 0.24	1.40 ± 0.25
Level of libido (4 = normal)	3.79 ± 0.13	3.73 ± 0.09	4.00 ± 0.11
Difficulty with ejaculation (4 = normal)	4.54 ± 0.20*	4.68 ± 0.22*	4.00 ± 0.01

All values are mean ± SEM. *Significant differences relative to placebo. Score scale ranged from 1 to 7 with higher scores indicating more pronounced side effects, except for level of libido and difficulty with ejaculation, where 4 = normal, 1 = no interest at all, and 7 = greatly increased.

Side-Effect Data

The side-effect questionnaire data are illustrated in **Table II**. With respect to sleep hygiene issues, there were significant main effects of drugs on 'getting to sleep' [$F(2,46) = 7.10$, $p < 0.002$], 'number of awakenings' [$F(2,46) = 5.16$, $p < 0.009$], and on 'difficulty returning to sleep' [$F(2,46) = 10.77$, $p < 0.0002$]. Post hoc analyses of these main effects indicates that relative to placebo, both citalopram and escitalopram created difficulty getting to sleep and difficulty returning to sleep after awakening, and that citalopram resulted in significantly more awakenings than placebo, but the awakenings due to escitalopram were not significantly different than those due to placebo.

There was a significant main effect of drugs for dry mouth [$F(2,46) = 8.17$, $p < 0.001$], and for nausea [$F(2,46) = 4.87$, $p < 0.01$], but not for diarrhea [$F(2,46) = 3.46$, $p < 0.06$]. Post hoc analysis of the main effect of drugs for dry mouth and nausea revealed that both citalopram and escitalopram caused more dry mouth and nausea than placebo. There was a significant drug × weeks interaction for nausea [$F(2,46) = 4.87$, $p < 0.012$]. Post hoc analysis of this interaction revealed that both drugs were nauseogenic for week 1 but not for week 2.

There was a significant main effect of drugs for tremors [$F(2,46) = 5.91$, $p < 0.005$], but not for sweating [$F(2,46) = 2.52$, $p < 0.09$]. Post hoc analysis of the main of effect of drugs on tremors revealed that relative to placebo, both citalopram and escitalopram resulted in more tremors. There was a significant main effect of drugs for drowsiness [$F(2,46) = 17.31$, $p < 0.00001$], but not for dizziness. Post hoc analysis of the main effect of drowsiness revealed that both citalopram and escitalopram caused more drowsiness than placebo.

With respect to sexual dysfunction, the main effect of drugs on difficulty with ejaculation [$F(2,28) = 7.04$, $p < 0.003$] was significant, but the main effect of drugs on libido was not. Post hoc analysis of the main effect of drugs on difficulty with ejaculation revealed that relative to placebo, both citalopram and escitalopram caused more difficulty with ejaculation.

DISCUSSION

In the current study, we found no effect of citalopram or escitalopram on performance measures including SRT, LRT, SST, Multitask, or any of the four MacWorth Clock Task data sets in short term administration in healthy subjects. The SRT, LRT, and SST tasks are traditional serial iterative tasks which have been used in the performance literature for decades. The Multitask has been in use in our laboratory for almost 10 yr and assesses aviation-relevant performance, including scores related to error detection and selective attention, visuo-motor tracking and coordination, short-term memory, mental arithmetic, and scanning strategies. This task provides higher validity for extrapolation of simulated laboratory flying performance to actual flight performance. The MacWorth Clock Task was developed to assess the vigilance performance of Royal Air Force radar operations in the 1940s. Riedel et al. (15) recently reported that citalopram impacted negatively on vigilance performance on the MacWorth Clock Task. Our data did not support this conclusion. We note that Riedel et al. used a single-tailed test which yielded a $p = 0.04$ level of significance. In our opinion, a 2-tailed test would have been more appropriate in analysis of their data, which would have resulted in a non-significant $p = 0.08$.

Subjects reported moderate increases in subjective sleepiness and fatigue due to citalopram and to escitalopram. However, these subjective symptoms did not translate into performance decrements, including vigilance. Our side-effect questionnaire data confirmed some of the previously known side effects attributable to citalopram and escitalopram (difficulty getting to sleep and difficulty returning to sleep after awakening, dry mouth, nausea, tremors, drowsiness, and difficulty with ejaculation), but found no increase in diarrhea, no increased sweating, no increase in dizziness, and no decrease in libido. Relative to placebo (0.92 ± 0.19 awakenings per night), citalopram resulted in a significant increase in awakenings (2.72 ± 0.52 awakenings per night), but escitalopram did not (1.76 ± 0.19 awakenings per night). Some of the side effects (e.g., nausea) had already started to abate during the second week of

administration. With long-term administration for treatment of depression, further attenuation of side effects would be anticipated. Consideration of return of aircrew to restricted flying duties would require careful aeromedical evaluation of adverse effects.

Our a priori experimental design calculations indicated that a sample size of 28 subjects was required in order to have a power of 80% to detect a 6% change in performance of our SUSOPS tasks (SRT, LRT, and SST). We were four subjects short of this recruiting target, so one limitation of our study is that our statistical power is somewhat short of 80%. Therefore, a type II error cannot be ruled out. Nevertheless, the results of the current study are consistent with previous work which indicates that selected antidepressant medications either have no impact on psychomotor performance (8), or improves it in spite of subjective reports of side effects, especially drowsiness (3–5) and sleep difficulties (3).

SSRI medications are often prescribed for a year or more in the treatment of a major depressive episode. In individuals with a second episode, treatment may extend for several years, if not indefinitely. With respect to the question of whether our findings can be extrapolated to aircrew being treated for depression whose depressive symptoms have resolved for many months, it is our opinion that such individuals are effectively no longer "depressed" and it is reasonable to extrapolate from findings in healthy subjects.

Conclusion

The current study found no impact of citalopram or of escitalopram on several traditional psychomotor tasks or on a complex task simulating flying performance. Some of our subjects experienced a number of expected side effects due to citalopram and escitalopram, including insomnia, drowsiness, and tremor. While these side effects did not translate into measurable performance effects, they may be of potential concern when considering a return to restricted flying duties while on maintenance doses of these medications. This study demonstrates the absence of citalopram and escitalopram effects on psychomotor performance in non-depressed subjects and supports the possibility of selected use in aircrew. These findings should be helpful in the still ongoing aeromedical discussion about this evolving issue (6).

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